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LETTER TO THE EDITOR

The challenges of diagnosing heparin-induced thrombocytopenia in patients with COVID-19

To the Editor,

Riker et al[1] published a report of three cases of heparin-induced thrombocytopenia (HIT) in patients with coronavirus disease 2019 (COVID-19). We would like to submit additional cases from our institution for consideration and discussion.

Differentiating severe COVID-19 and HIT presents multiple challenges. First, the diagnosis of HIT is complex and requires multiple tools (clinical probability score [4Ts score], enzyme immunoassays [EIAs] and functional assays such as the serotonin release assay [SRA]), each with varying sensitivity and specificity. Second, similar to HIT, COVID-19 increases thrombotic risk[2] and thrombocytopenia can occur as patients become critically ill. Finally, it is recommended that all COVID-19 hospitalized patients receive heparin thromboprophylaxis.[2]

In the cases presented by Riker et al,[1] only one patient was diagnosed with HIT based on a positive SRA. Two had positive EIAs, intermediate- or high-risk 4Ts scores, but negative SRAs. We disagree with the authors' conclusion that the latter SRAs were falsely negative. Instead, we suspect that the EIAs were falsely positive considering the patients' thrombosis and thrombocytopenia could be otherwise explained by severe COVID-19.

EIAs are sensitive, but not specific, for HIT diagnosis because they detect *all* anti–platelet factor 4 (PF4)/heparin antibodies, including those that are nonpathogenic.[3] In contrast, functional assays (including SRA) identify only antibodies with the pathogenic ability to activate platelets and therefore have increased specificity.[3] Given that severe COVID-19 is a hyperinflammatory state, it is plausible that the increased immunoreactivity also increases production of anti-PF4/heparin antibodies; however, they may not result in clinical HIT but may instead increase potential for false-positive EIAs.

Herein, we report our experience with hospitalized patients with COVID-19 with positive HIT EIAs (Asserachrom HPIA ELISA Kit, Diagnostica Stago, Parsippany, NJ, USA) (Table 1). Only one of seven was diagnosed with HIT based on a positive SRA (Versiti, Milwaukee, WI, USA). Patient 6 had a high-probability 4Ts score, but given the low EIA optical density and negative SRA, the patient was determined to not have HIT. All other patients were interpreted as having false-positive EIAs due to low- or intermediate-risk 4Ts scores and negative SRAs.

Misdiagnosing HIT in patients with COVID-19 has important clinical implications. Evidence suggests that heparin has anti-inflammatory and anti-infectivity properties in COVID-19, raising concern that switching to nonheparin anticoagulants loses these benefits. Furthermore, other intravenous anticoagulants are more difficult to monitor, potentially increasing the risk of bleeding or progressive thrombosis, along with increasing cost. Finally, a HIT diagnosis is lifelong and would preclude all future heparin exposures.

These cases highlight the challenges of diagnosing HIT in patients with COVID-19. Further studies are needed in the COVID-19 population to determine the frequency of HIT, the frequency of nonpathogenic anti-PF4/heparin antibodies, and the best tools to confirm/refute the diagnosis. In the interim, we propose that a functional assay such as SRA be included whenever possible in the evaluation of all patients with positive EIA given the clinical similarity between HIT and COVID-19 along with the potential for false-positive EIA results.

RELATIONSHIP DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

JEM performed data collection and analysis and participated in conceptualization and writing of the manuscript. RCS and MM participated in conceptualization and editing of the manuscript.

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TABLE 1 COVID-19 patients with positive HIT EIA at a large academic medical center

Patient	Age	Sex	Race	Heparin exposure	Indication	Thrombosis?	Platelet nadir (10^9/L)	4Ts		EIA OD	SRA result	HIT diagnosis?	Outcome
								Score	Risk				
1	50	M	AA	UFH SQ UFH IV	Prophylaxis ECMO	No	49	5	Intermediate	0.626	Negative	No	Death
2	79	F	W	LMWH	Prophylaxis	No	155	3	Low	1.881	Negative	No	Discharge
3	58	F	AA	LMWH	Prophylaxis	PTE	305	3	Low	0.505	Negative	No	Death
4	61	F	AA	UFH IV	CRRT	No	37	4	Intermediate	0.950	Positive	Yes	Pending
5	38	M	W	LMWH UFH IV	Prophylaxis ECMO	No	39	3	Low	0.828	Negative	No	Pending
6	71	F	AA	UFH SQ UFH IV	Prophylaxis CRRT	Stroke	70	6	High	0.465	Negative	No	Death
7	46	M	AA	LMWH	Prophylaxis	DVT	59	5	Intermediate	0.828	Negative	No	Pending

Abbreviations: AA, African American; CRRT, continuous renal replacement therapy; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; EIA, enzyme immunoassay; F, female; LMWH, low-molecular-weight heparin; M, male; OD, optical density; PTE, pulmonary thromboembolism; SRA, serotonin release assay; UFH, unfractionated heparin; W, White.

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